one end of a tether and another end of the tether is covalently linked to the substrate. The growth effector molecules can freely interact with the cell but are not internalized by the cell.

The effectiveness of the growth effector molecules on the rate of cell growth is maintained, and in fact enhanced, because the growth effector molecules are tethered on the ends of flexible, water soluble, tethers that provide mobility to the molecules sufficient for the molecules to contact receptors in the cell membrane, but without allowing internalization of the molecules. The polymers of the claimed methods are able to extend to their full length, providing a wide range of movement (flexibility) to the factors attached thereto. Additionally, the tethers will not interact with the cell. This attribute also allows free movement of the molecules so that the molecules can contact the cell receptors and allow aggregation of growth effector molecule/receptor complexes on the cell membrane. (*See* the Specification at page 5, line 24 through page 6, line 10)

The molecules are attached in a concentration effective to enhance the rate of growth of the target cells. The amount and types of tethers must be properly balanced with the amounts of growth effector molecules to achieve an enhanced growth rate. Applicants show how to enhance the rate of cell growth by balancing use of polymeric tethers which do not bind to cells and the use of the proper amounts of tethered growth effector molecules.

Rejection Under 35 U.S.C. § 102

The Examiner has reiterated the prior art rejections that were vacated by the Decision of the Board of Patent Appeals and Interferences. Claims 14-17 were rejected under 35 U.S.C. §

102(b) as being anticipated by WO 89/05616 by Bio-Metric Systems, Inc. ("WO '616"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

WO '616

WO '616 does not teach every limitation of the claimed methods. WO '616 generally discloses the use of polymeric spacers to distance a biomolecule from a substrate. Among the biomolecules mentioned are some of the growth effector molecules claimed by Applicants. However, the only examples in WO '616 involving cells demonstrate tethering of collagen, hyaluronic acid, and fibronectin (Examples 3 and 6). WO '616 does not report enhanced **growth** of cells but only enhanced **adhesion** as recognized at page 24, "The cells preferentially attached to the modified surface versus control surfaces, as indicated by the distance they grew out over the plastic surface."

WO '616 does not teach how to tether growth effector molecules to enhance cell growth. WO '616 teaches the use of PEO (a polymer commonly grafted to surfaces to inhibit cell adhesion), and generally teaches high concentrations of tether with no specifics about how to cause cell adhesion in the presence of this type of tether so as to avoid rounding up and non-adherent cells. Applicants show how to enhance the rate of cell growth as compared to the rate of cell growth with soluble or adsorbed molecules by balancing use of polymeric tethers which do not bind to cells with the use of the proper amounts of tethered growth effector molecules.

WO '616 teaches how to tether proteins, but not how to tether growth effector molecules so that cell growth will be enhanced.

WO '616 discloses only linear polymeric tethers having one end attached to a support and the second end attached to a biomolecule. In other words, WO '616 does not teach or suggest that the tethers can bind more than one biomolecule, as encompassed by the claims as pending This is an important aspect of the claimed compositions and methods, as discussed in the application on page 7, lines 3-8 and page 12, lines 25-28. As claimed, the tethers can bind more than one molecule of the same growth effector or can bind different types of growth effector molecules. Thus, the density of a growth effector molecule on a substrate can be increased without substantially increasing the number of cell-repellant tethers. Alternatively, for example, both insulin and EGF could be tethered to the same substrate, allowing presentation of two or more growth effector molecules to the cell.

Under the approach outlined in WO '616, in theory any concentration of molecules could be attached. However, since only linear tethers, i.e. tethers with only one attachment site for a factor and one attachment site to the substrate, are used, going to lower concentrations also increases the distance between factors and potentially inhibits the ability of receptor-factor complexes to interact in the cell membrane. Thus, at lower concentrations, signaling may not occur at all using linear tethers, because the factors are homogeneously spaced on the surface. By using a multi-functional flexible tether, Applicants can go to very low factor concentrations and still allow receptor aggregation by virtue of having more than one factor on each tether.

Even though the tethers can be very far apart (i.e. the distance from the center of one tether to the center of the adjacent tether can be more than twice the fully extended chain length of the tether), receptor-receptor interactions can still occur in the membrane after ligand-binding because the factors are locally clustered. Thus, WO '616 does not teach the inclusion of growth effector molecules, nor the inclusion of both polymeric tethers and growth effector molecules in a concentration effective to enhance the rate of target cell growth. Therefore, claims 14-17, as amended, are novel over WO '616.

Rejection Under 35 U.S.C. § 103

The Examiner has reiterated the prior art rejections that were vacated by the Decision of the Board of Patent Appeals and Interferences. Claims 14-16 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,370,681 to Herweck et al. ("Herweck"), in combination with U.S. Patent No. 5,171,264 to Merrill ("Merrill '264"). Claim 17 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck in combination with Merrill '264 in combination with U.S. Patent No. 5,522,895 to Mikos *et al.* ("Mikos"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Herweck

Herweck discloses implantable devices for sustained release of a bioactive material, such as a therapeutic agent, a cell type, or a diagnostic agent, into a fluid flow pathway of a patient (see column 3, lines 14-16 and 30-37). Herweck discloses first coating or modifying the surface with glycoproteins such as fibronectin prior to seeding the device with cells (see column 4, lines

62-68). Herweck discloses that such coating may result in improved adhesion of cells (see column 6, lines 23-29). As recognized by the Examiner, Herweck does not disclose or suggest the use of a tether attaching a growth effector molecule to a substrate but merely coats, or adsorbs, the factor upon the substrate.

Merrill '264

Merrill '264 discloses star molecules of polyethyleneoxide (PEO) that are biocompatible and demonstrate non-thrombogenic properties. Merrill '264 discloses the type of star molecules that are useful in Applicants' methods, as discussed in the specification at page 7, lines 3-20. However, Merrill '264 does not teach the inclusion of growth effector molecules.

The combination of Herweck and Merrill '264

There is no suggestion in either reference to incorporate the teaching of the other reference. Herweck does not suggest that it would be advantageous to tether the factors to the substrate. Merrill '264 does not suggest using the star molecules for tethering growth effector molecules to a substrate. The primary use for the star molecules that is described in Merrill '264 is for separating and purifying therapeutic proteins. Other proposed uses are described at Merrill '264, column 6, lines 6-27.

Moreover, even if the teachings of the references are combined, the combination does not suggest the claimed compositions or methods because it does not suggest attaching growth effector molecules with tethers to a substrate in a concentration effective to enhance cell growth. Merrill does not suggest how to tether growth effector molecules to alter cell growth. Even if

one of skill in the art used PEO tethers in the device taught by Herweck in order to **prevent** thrombogenesis, as suggested by the Examiner, there is no teaching in the references on how to do so to **enhance** cell growth.

In fact, Merrill '264 teaches away from the claimed compositions and methods because it discloses that the PEO star molecules are non-thrombogenic, i.e., do not absorb proteins of the intrinsic clotting system or of the platelet membrane (see Merrill '264, col. 1, lines 6-9). One of ordinary skill in the art would thus know that the use of PEO as a tether would tend to repel cells, and would believe that PEO would not allow contact of the attached growth effector molecules with the cells. In contrast, Applicants use polymeric tethers, such as PEO, in the claimed methods, and the growth effector molecules are able to contact cells so as to provide enhanced cell growth.

There is no teaching in either reference to select growth effector molecules in the amount required to enhance growth rate when not internalized by the cells. Further, neither reference teaches nor suggests chemically coupling the growth effector molecules to a substrate in a density and with appropriate linkers to result in enhanced growth rates of attached cells. Thus, claims 14-16 are non-obvious over Herweck in view of Merrill '264.

Mikos

Mikos is similar to Herweck, in that it is directed to a matrix for seeding with cells that can be implanted. Mikos also does not disclose or make obvious selecting growth effector molecules, determining the amount required to enhance growth rate when not internalized, nor

chemically coupling the molecules to the substrate in a density and with appropriate linkers to result in enhanced growth rates of attached cells.

The combination of Herweck with Merrill '264 and Mikos

Claim 17 is dependent upon claim 14 which, as discussed above, is not taught nor made obvious by Herweck and Merrill '264. Mikos does not add the elements missing from the Herweck/ Merrill combination. Therefore, claim 17 is non-obvious over Herweck in view of Merrill '264 and Mikos.

Double Patenting Rejection

Claims 14-17 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,906,828 to Cima *et al.* Claim 32 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 20 of U.S. Patent No. 6,045,818 to Cima *et al.* Applicants respectfully traverse these rejections.

Two-Way Double Patenting

M.P.E.P. § 804 (B) (1) (b) describes situations under which it is appropriate to require a two-way test for obviousness-type double patenting. Two conditions must be met: (1) the applicant could not have filed the claims in a single application and (2) the PTO controlled the rates of prosecution, which caused delay in the issuance of the earlier filed application.

Applicants meet both conditions. First, Applicants were unable to pursue the claims of U.S. Patent Nos. 5,906,828 and 6,045,818 in the present application. For example, Applicants

proposed an amendment to the claims so they would correspond with the claims in U.S. Patent No. 5,906,828. In the Amendment and Response filed September 4, 1997, Applicants proposed to amend the claims to further define the biocompatible polymeric tethers as being branched and water soluble and to state that the tethers are able to covalently link to more than one growth factor (*see* September 4, 1997 Amendment and Response, claims 1, 8, 31, and 32) Applicants further proposed to amend the claims to define the rate of target cell growth as being greater than the rate of target cell growth in soluble growth effector molecules and growth effector molecules that are adsorbed to a substrate. (*Id.*) **However, the Examiner refused to enter this amendment** (*see* September 16, 1997 Advisory Action).

In response, Applicants filed a Notice of Appeal and a Petition for Entry of the Amendment on September 24, 1997. In the Petition, Applicants explained that the amendment should have been entered because it did not raise any new issues which would require further consideration and/or search and it reduced the number of issues for appeal. **However, the Petition was denied**. Though the Director agreed with Applicants' assertions that the "proposed amendments would not necessarily require further search or raise the issue of new matter", he denied the petition because the proposed amendments would require further consideration by the Examiner (see Decision on Petition mailed December 15, 1997). Thus, Applicants were unable to pursue the claims which correspond with the claims in U.S. Patent No. 5,906,828.

Applicants also meet the second condition. The delay by the U.S. PTO caused two continuation patent applications to issue before the pending application. The appeals process

lasted for over 4 years. U.S. Patent Nos. 5,906,828 and 6,045,818 issued on May 25, 1999 and April 14, 2000, respectively. Due to the delay caused by the appeals process, U.S. Patent Nos. 5,906,828 and 6,045,818 issued before a Decision on Appeal was even rendered. Had the U.S. PTO been able to render a decision more quickly, Applicants could have amended the claims in the pending application and may not have needed to file either of the continuation applications. Since Applicants meet both requirements, a two-way obviousness test should be required. However, as noted by the Examiner, the claims of U.S. Patent Nos. 5,906,828 and 6,045,818 are not obvious in view of the pending claims. Therefore, the obviousness-type double-patenting rejection is improper.

Allowance of claims 14-17 and 32, as amended, is respectfully solicited.

Respectfully submitted,

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AMENDMENT AND RESPONSE TO OFFICE ACTION

Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, August 21, 2002 to the Commissioner for Patents, U.S. Patent and Trademark Office, Washington, DC 20231.

Aisha Wyatt

Date: August 21, 2002

Marked Up Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

Please cancel claims 1-13.

14. (Amended) A method for growing eukaryotic cells comprising

bringing into contact the cells and a composition comprising

a biocompatible solid substrate,

biocompatible polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules; and

maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow,

wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

15. The method of claim 14 wherein the composition is administered by injection, infusion, or implantation.

16. The method of claim 15 wherein the composition is administered by implantation of the composition and wherein the substrate is shaped to match a desired tissue shape.

17. The method of claim 16 wherein the substrate is biodegradable.

Please cancel claims 18-31.

32. (Amended) A method of testing a compound for an effect on tissue comprising bringing into contact the compound to be tested and a composition comprising

a biocompatible solid substrate,

biocompatible polymeric tethers,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules, and wherein the growing cells are bound to the growth effector molecules;

incubating the compound and the composition under conditions promoting cell growth; and

observing the cells for any effect not observed in cells not brought into contact with the composition.

Clean Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

14. (Amended) A method for growing eukaryotic cells comprising

bringing into contact the cells and a composition comprising

a biocompatible solid substrate,

biocompatible polymeric tethers, and

growth effector molecules,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules; and

maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow,

wherein the step of bringing into contact comprises administering the composition to a patient in need of cell growth.

15. The method of claim 14 wherein the composition is administered by injection, infusion, or implantation.

16. The method of claim 15 wherein the composition is administered by implantation of the composition and wherein the substrate is shaped to match a desired tissue shape.

17. The method of claim 16 wherein the substrate is biodegradable.

32. (Amended) A method of testing a compound for an effect on tissue comprising bringing into contact the compound to be tested and a composition comprising

a biocompatible solid substrate,

biocompatible polymeric tethers,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate and each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth without internalization of the molecules, and wherein the growing cells are bound to the growth effector molecules;

incubating the compound and the composition under conditions promoting cell growth; and

observing the cells for any effect not observed in cells not brought into contact with the composition.